Administration of influenza vaccines to patients with egg allergy: Update for the 2010-2011 season

To the Editor:

The practice parameter on adverse reactions to vaccines published in 2009 stated, "For influenza vaccine in egg-allergic patients, if the egg protein content of the vaccine is known to be <1.2 mcg/mL, administer 10% of the dose, followed in 30 minutes by the remaining 90%, or as a single dose."[1] In a recent editorial this author argued strongly for the administration of influenza vaccines to patients with egg allergy because the risk of not vaccinating far outweighs the risk of vaccinating.[2] None of the brands of influenza vaccine for the 2009-2010 season were shown to contain ovalbumin in excess of that found to be safe for administration to patients with egg allergy.[3,4] Although in theory it seems prudent to choose a brand with a lower amount of egg protein to reduce the chances of a reaction,[2] several recent publications have appeared that present additional considerations when choosing a particular influenza vaccine for a patient with egg allergy.

Afluria (CSL Limited, Parkville, Victoria, Australia), which has a low ovalbumin content (≤1 μg/0.5-mL dose), was initially approved for persons aged 6 months and older[5]; however, because of an increased risk of febrile seizures, the vaccine is now recommended only for those aged 9 years and older.[6]

Fluarix (GlaxoSmithKline, Research Triangle Park, NC) and Fluvirin (Novartis, Cambridge, Mass) have low ovalbumin content (≤0.05 μg/0.5-mL dose and ≤1 μg/0.5-mL dose, respectively), but the 2010-2011 package inserts and recently published studies indicate that the vaccines showed decreased immune responses compared with other influenza vaccines in children less than 3 and 4 years of age, respectively.[7-9] The other 2 influenza vaccines by these same manufacturers, FluLaval (GlaxoSmithKline) and Agriflu (Novartis), also have low ovalbumin content (≤1 μg/0.5-mL dose and <0.4 μg/0.5-mL dose, respectively) but have not been studied in patients less than 18 years of age.[10,11]

An influenza vaccine with one of the lowest absolute amounts of ovalbumin per dose is the live attenuated influenza vaccine FluMist (MedImmune, Gaithersburg, Md). The package insert for this vaccine[12] does not state the ovalbumin content, but the manufacturer indicates that the ovalbumin content is less than 0.24 μg/0.2-mL dose (personal communication, August 10). However, there are no data on its administration to patients with egg allergy nor any data on exposure to egg proteins through the respiratory route. It cannot be administered to patients with asthma (which often coexists with egg allergy) because of an increased risk of asthmatic events when the vaccine was administered in safety studies.[12] It has also been associated with an increased rate of hospitalization in children younger than 24 months, and effectiveness has not been proved in patients older than 49 years.[12]

The vaccines with the highest amount of ovalbumin are Fluzone and Fluzone High-Dose (Sanofi Pasteur, Swiftwater, Pa).[2-4] The combined package insert for these vaccines[13] does not state the ovalbumin contents, but the manufacturer indicates that the ovalbumin content is less than 5 μg/0.5-mL dose for Fluzone and, because of differences in the manufacturing process, less than 1.6 μg/0.5-mL dose for Fluzone High-Dose (personal communication, October 2010).

When these vaccines have been assayed in independent research laboratories, although the ovalbumin content in Fluzone is higher than that in the other brands, all are typically 10-fold or more less than the manufacturer's stated maximum levels.[3,4]

For patients with egg allergy older than 3 years, the choice of Fluarix seems most appropriate because it has been approved for this age group and has a low ovalbumin content. For those older than 4 years, Fluvirin would be an additional choice for the same reasons. After age 9 years, a third choice would be Afluria because it also has low ovalbumin content, and this is beyond the age when febrile seizures have been an issue. After 18 years of age, FluLaval and Agriflu would be 2 additional choices, again because of low ovalbumin content.

For children with egg allergy between 6 and 23 months of age, the choice of influenza vaccine is more difficult. The only influenza vaccine approved in this age group is Fluzone, the vaccine with the highest ovalbumin content. For children with egg allergy between 24 and 35 months of age who do not have asthma, another possible choice is FluMist. It has low ovalbumin content, but exposure through the respiratory route has not been studied.

All of these are relative considerations; some vaccines are less immunogenic but still generate adequate immune responses in the majority of recipients, and the vaccines associated with higher rates of febrile seizures or hospitalization do not lead to these outcomes in the vast majority of recipients. Nonetheless, it seems prudent to avoid vaccines with these possible shortcomings. However, this means choosing a vaccine that might be more likely to cause an allergic reaction in a child with egg allergy. However, the amount of egg protein, even in the vaccine with the highest ovalbumin content (Fluzone), is very unlikely to lead to an adverse outcome because the actual amount of ovalbumin in the vaccine in recent years is less than that administered uneventfully, even to patients with severe egg allergy.[14] Similarly, although there are no data on use of the intranasal route of influenza vaccine administration in children with egg allergy, this vaccine (FluMist) has low ovalbumin content and again is very unlikely to lead to an allergic reaction.

Any risk associated with administering egg-containing vaccines to patients with egg allergy can be mitigated by doing so in a setting in which anaphylaxis can be recognized and treated, should it occur, with an observation period of at least 30 minutes after vaccine administration. Other measures to try to mitigate this risk have included skin testing with the vaccine or giving it in divided doses. In the study by James et al[14] demonstrating that even patients with severe egg allergy could safely receive an influenza vaccine containing up to 1.2 μg/mL ovalbumin (≤0.6 μg/0.5-mL dose), vaccine skin test results were positive in only a few patients, and the vaccine was administered uneventfully even to those with positive vaccine skin test results. Another recent study by Chung et al[15] found that the percentage of children with egg allergy who tolerated the influenza vaccine was the same whether vaccine skin tests were (94.6%) or were not (96.5%) performed before vaccination and concluded that vaccine skin testing in this setting was unnecessary. The study excluded patients with histories of recent egg-induced anaphylaxis, and the ovalbumin contents of the vaccines used were not measured. Similarly, it is

TABLE I. Choice of influenza vaccine for patients with egg allergy, 2010-2011 season

Manufacturer	CSL Behring	GlaxoSmithKline		MedImmune	Novartis		Sanofi Pasteur	
Brand	Afluria	Fluarix	FluLaval	FluMist	Fluvirin	Agriflu	Fluzone	Fluzone High-Dose
Ovalbumin content (μg/dose)*	Low	Low	Low	Low	Low	Low	Higher	Higher
Manufacturer's claims†	≤1	≤0.05	≤1	<0.24	≤1	<0.4	<5	<1.6
Independent assays‡	0.009-0.011	<0.025	<0.05	<0.001-0.004	<0.025		<0.1-0.711	
Age								
<6 mo	Influenza vaccine not recommended							
6-23 mo	Increased risk of febrile seizures	Decreased immune response	Not studied	Increased hospitalization	Decreased immune response	Not studied	Approved‖	Not studied
24-35 mo				Approved (if no asthma)§				
36-47 mo		Approved						
4-8 y					Approved			
9-17 y	Approved							
18-49 y			Approved			Approved		
50-64 y				Not effective				
≥65 y								Approved‖

*Per 0.5-mL dose, except FluMist per 0.2-mL dose.
†Per package inserts, except FluMist and Fluzone and Fluzone High-Dose by personal communication.
‡Of 2009-2010 formulations.[3,4]
§No data on use in patients with egg allergy.
‖Higher ovalbumin content.

not clear that dividing the dose is necessary. In the James et al[14] study, only 3 of 83 patients with egg allergy had a systemic reaction to 10% of the dose (1 with wheezing and 2 with hives), and they uneventfully received the remaining 90% thirty minutes later nonetheless. In the Chung et al[15] study 6 of 171 patients with egg allergy had some reaction to 10% of the dose (wheezing, eczema exacerbation, or hives), and the remaining 90% was withheld. In a more recent study by Gagnon et al,[16] investigators administered influenza vaccine containing 0.008 μg of ovalbumin per 0.5-mL dose to 830 patients with confirmed egg allergy, and more than 3,600 with reported egg allergy without vaccine skin testing, dividing the dose (10%/90%) only in those with a history of respiratory or cardiovascular reactions after egg ingestion, and had no cases of anaphylaxis. Although not studied directly, both James et al[14] and Gagnon et al[16] noted that because all patients went on to receive the 90% dose without serious reactions, those who received the vaccine in divided doses would likely have tolerated the full dose as a single injection.[14,16]

Studies administering Fluzone (highest ovalbumin content) and FluMist (low ovalbumin content but nasal route) to patients with egg allergy without prior vaccine skin testing and without dividing the dose are being conducted to evaluate the safety of this approach. Until results of these studies are available, practitioners will need to weigh the risks and benefits of various vaccines and, in discussion with patients and families, decide which vaccine to administer on an individual basis. Another possible choice is not vaccinating at all, but the risk of disease in unvaccinated persons would seem to far outweigh any risk of vaccination.[2] Many clinics and hospitals purchase influenza vaccine from only 1 or a limited number of manufacturers, which might further limit the choices of vaccine available.

The influenza vaccines available for the 2010-2011 influenza season in the United States are listed in Table I, along with the ovalbumin content and considerations for each vaccine in each age group regarding effectiveness and side effects. It would seem reasonable to first choose a vaccine that is approved for a given age group and then choose one (among those approved for a given age group) with low ovalbumin content, if available. As above, skin testing with the vaccine is not necessary. If a low-ovalbumin vaccine is not available or in patients with a history of particularly severe reactions to egg ingestion, some might choose to administer the vaccine in divided (10%/90%) doses. It should also be noted that an even more conservative approach, including vaccine skin testing and administration by means of a multidose protocol is appropriate for those rare patients with a history of an allergic reaction to influenza vaccine administration itself, as opposed to the much more common patients addressed in this update with a history of an allergic reaction to egg ingestion but no history of reaction to influenza vaccine administration.

John M. Kelso, MD

From the Division of Allergy, Asthma and Immunology, Scripps Clinic, San Diego, Calif. E-mail: kelso.john@scrippshealth.org.

Disclosure of potential conflict of interest: J. M. Kelso has declared that he has no conflict of interest.

REFERENCES

1. Kelso JM, Li JT, Nicklas RA, Blessing-Moore J, Cox L, Lang DM, et al. Adverse reactions to vaccines. Ann Allergy Asthma Immunol 2009;103(suppl):S1-S14.
2. Kelso JM. Administration of influenza vaccines to patients with egg allergy. J Allergy Clin Immunol 2010;125:800-2.
3. Waibel KH, Gomez R. Ovalbumin content in 2009 to 2010 seasonal and H1N1 monovalent influenza vaccines. J Allergy Clin Immunol 2010;125:749-51, e1.
4. Li JT, Rank MA, Squillace DL, Kita H. Ovalbumin content of influenza vaccines. J Allergy Clin Immunol 2010;125:1412-3.
5. Fiore AE, Uyeki TM, Broder K, Finelli L, Euler GL, Singleton JA, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Recomm Rep 2010;59:1-62.

6. Update. recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding use of CSL seasonal influenza vaccine (Afluria) in the United States during 2010-11. MMWR Morb Mortal Wkly Rep 2010;59:989-92.
7. FLUARIX (influenza virus vaccine) 2010-2011 formula [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2010.
8. FLUVIRIN (influenza virus vaccine) 2010-2011 formula [package insert]. Cambridge, Mass: Novartis; 2010.
9. Baxter R, Jeanfreau R, Block SL, Blatter M, Pichichero M, Jain VK, et al. A Phase III evaluation of immunogenicity and safety of two trivalent inactivated seasonal influenza vaccines in US children. Pediatr Infect Dis J 2010;29:924-30.
10. FLULAVAL (influenza virus vaccine) 2010-2011 formula [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2010.
11. AGRIFLU (influenza virus vaccine) 2010-2011 formula [package insert]. Cambridge, Mass: Novartis; 2010.
12. FluMist (influenza vaccine live, intranasal) 2010-2011 formula [package insert]. Gaithersburg (MD): MedImmune; 2010.
13. Fluzone (influenza virus vaccine) Fluzone high-dose (influenza virus vaccine) 2010-2011 formula [package insert]. Swiftwater, Pa: Sanofi Pasteur; 2010.
14. James JM, Zeiger RS, Lester MR, Fasano MB, Gern JE, Mansfield LE, et al. Safe administration of influenza vaccine to patients with egg allergy. J Pediatr 1998;133:624-8.
15. Chung EY, Huang L, Schneider L. Safety of influenza vaccine administration in egg-allergic patients. Pediatrics 2010;125:e1024-30.
16. Gagnon R, Primeau MN, Des Roches A, Lemire C, Kagan R, Carr S, et al. Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine. J Allergy Clin Immunol 2010;126:317-23.

doi:10.1016/j.jaci.2010.10.015

Successful engraftment of donor marrow after allogeneic hematopoietic cell transplantation in autosomal-recessive hyper-IgE syndrome caused by *dedicator of cytokinesis 8* deficiency

To the Editor:

The hyper-IgE syndromes are rare combined immune deficiencies associated with marked elevations in plasma IgE levels and eosinophilia. An autosomal-dominant form of hyper-IgE syndrome caused by mutations in *signal transducer and activator of transcription 3* is characterized by elevated IgE, eosinophilia, eczema, recurrent skin and pulmonary infections, and skeletal abnormalities.[1] Recently, an autosomal recessive form of hyper-IgE syndrome caused by mutations in the *dedicator of cytokinesis 8 (DOCK8)* gene has been identified and is characterized by elevated IgE levels, eosinophilia, atopic dermatitis, asthma, food allergies, recurrent upper and lower respiratory tract infections, and unusual susceptibility to infections with herpesvirus family members (herpes simplex virus, human papilloma virus) and molluscum contagiosum.[2,3] Cutaneous infections with human papilloma virus have progressed to squamous cell carcinomas in some cases. Immunologic evaluation of *DOCK8*-deficient patients has revealed T-cell lymphopenia with impaired proliferative responses of both $CD4^+$ and $CD8^+$ T cells as well as impaired differentiation of T_H17 T cells.[2-4]

We report a case of an 8-year-old girl, born to first-degree cousins, who initially presented with pneumococcal meningitis at 11 months of age, complicated by chorda tendineae rupture and flail mitral valve. Isolated asplenia was noted during imaging. She later began to have recurrent episodes of upper and lower respiratory tract infections, pneumococcal bacteremia, giardiasis, and cutaneous infections with herpes simplex virus and *Staphylococcus aureus*. She also developed flat warts thought to be a result of human papilloma virus infection. Complete blood count revealed hypereosinophilia that ranged from 11,020 to 49,700 cells/μL (Table I) for which she was treated with corticosteroids because of concerns of possible cardiac involvement. Bone marrow examination ruled out a leukemic process. The patient developed moderate persistent asthma and mild eczema. She had multiple food allergies, elevated total IgE (Table I), and positive specific IgE to milk, egg, fish, peanuts, and tree nuts. The patient had received immunization with tetanus toxoid and 23-valent pneumococcal polysaccharide vaccine (Pneumovax, Merck, Whitehouse Station, NJ) and had protective antibody titers to tetanus toxoid and to 6 of 14 pneumococcal serotypes tested. However, titers waned by age 5 years 6 months, and she failed to respond to Pneumovax booster given at age 6 years (see this article's Table E1 in the Online Repository at www.jacionline.org). Her T-cell numbers decreased over time, whereas her B-cell numbers were elevated (see this article's Table E2 in the Online Repository at www.jacionline.org). T-cell proliferation to mitogens and antigens was mildly diminished (see this article's Table E3 in the Online Repository at www.jacionline.org). Serum IgG levels fell over time, and the patient was started on intravenous immunoglobulin replacement therapy at age 7 years. Her clinical presentation prompted an evaluation for *DOCK8* deficiency. Western blot of lysates from PBMCs and an EBV-immortalized B-cell line revealed absence of DOCK8 protein (Fig 1, *A*). PCR amplifying genomic DNA revealed a deletion of exons 28 to 35 of the *DOCK8* gene (Fig 1, *B*).

TABLE I. Eosinophil counts and IgE levels

Age	Absolute eosinophil count (cells/μL)	IgE (U/mL)
10 mo	1,020	ND
2 y 7 mo	49,700	ND
3 y 8 mo	22,390	ND
4 y	21,710	930
6 y 8 mo	22,450	1,340
7 y 1 mo	13,340	574
7 y 10 mo	20,730	1,287

ND, Not determined.

Although experience with *DOCK8* deficiency is limited, its long-term prognosis is poor. Many *DOCK8*-deficient patients have disfiguring molluscum or human papilloma virus infections or die from fatal infections, squamous cell cancers, or lymphoma.[2] Therefore, the decision was made to perform allogeneic hematopoietic cell transplantation (HCT) for definitive correction of her combined immune deficiency. The patient was conditioned with 16 doses of busulfan intravenously adjusted to achieve levels of 800 to 1200 μmol/min on days –9 to –6 and 4 doses of cyclophosphamide 50 mg/kg intravenously on days –4 to –1 without incident. She received unmanipulated bone marrow containing 10×10^6/kg $CD34^+$ cells from her fully matched unaffected younger brother. Cyclosporine A and short-course methotrexate were given for graft-versus-host disease prophylaxis, and she received standard antiviral and antifungal prophylaxis. Neutrophil engraftment occurred on day +16 followed by a rapid rise in lymphocyte count to 4490 cells/μL on day +21. She was febrile and tachypneic with evidence of pulmonary edema with no organisms recovered from nasal secretions or sputum. Cell type–specific chimerism studies on day +21 post-HCT revealed that 100% of $CD3^+$ cells (3536 cells/μL) and 100% of $CD15^+$ cells (6210 cells/μL) were of